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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,845	11/19/2003	Ruth A, Gjerset	066732-0035	9478

7590 07/28/2005

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,845	GJERSET ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 19 November 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040903.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The claims are directed to a "bicistronic" The specification does not provide a special definition for this term. Although this term is often used in reference to an expression cassette that comprises two open reading frames (coding sequences for two proteins) separated by an internal ribosome entry site (IRES) under control of a single promoter, the term "bicistronic" is also used more generally to refer to expression vectors, which are constructs, that contain two open reading frames or coding sequences of interest, each under control of a separate promoter, i.e. a vector with two separate expression cassettes. See e.g. US 2002/0168739, Fig. 1A and ¶ 0027, which describes Fig. 1A. Consequently, the term "bicistronic construct" is interpreted to broadly mean a polynucleotide comprising p53 and p14ARF coding sequences under control of either the separate promoters or the same promoter, in which case the coding sequences are separated by an IRES.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required. The specification provides no antecedent basis for the liver, brain, kidney, "skim" (sic), ovarian or prostate tumor cells recited in claim 14.

Claim Objections

Claims 2, 4-6, 8, 11 and 14 objected to because of the following informalities: Claims 2, 4, 6, 8, and 11 are improperly punctuated – claim 6, double commas; claims 2, 4, 8 and 11, spaces before commas. In claim 4, line 2; claim 5, line 2; and claim 6, lines 1-4 (3 occurrences), "genes variants" should be --gene variants--.In claim 14, line 3, "skim" should be --skin--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14 are directed to bicistronic constructs that comprise a p53 gene and a p14ARF gene or "gene variants thereof." Claims 7-14 require the "gene variants" to express protein having tumor suppressor activity. The only description of "gene variants" for either p53 or p14ARF states that they are "variants of p53 or p14ARF (such as mutated or truncated forms of these tumor suppressors) that retain the tumor suppressor activity of the protein, or that display enhanced tumor suppressor activity" (page 6, lines 26-29). The specification does not provide

any structural information regarding such "gene variants" whose products retain tumor suppressor activity, much less that display enhanced tumor suppressor activity, nor is there evidence of record that such variants or their structure were well known in the prior art.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Unlike the situations reviewed by the courts and the Board, the instant specification does not even describe how one might isolate or make the recited "gene variants". Consequently, the specification does not provide an adequate written description of

"gene variants" of p53 and p14ARF genes to allow one of skill in the art to recognize that Applicant was in possession of the "gene variants" required by the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Depinho, R.A., US 2002/0193325.

Depinho discloses an expression vector comprising nucleic acids encoding p19ARF and p53, pharmaceutical compositions comprising the vector, and methods for treating tumor cells *in vitro* or cancer in patients with the vector. The vector can be a naked DNA vector or viral vector based upon HSV, adenovirus, or AAV, or can be delivered to tumor cells in a liposomal formulation. Cancers that can be treated include melanoma, bladder carcinoma, oral carcinoma,, lung carcinoma, and lymphoid neoplasms such as B-cell chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas. p19ARF is the murine homolog of p14ARF (Tango et al., Hum. Gene Ther. 13 :1373-1382, 2002, at page 1373 col. 2), i.e. it is a "gene variant" of p14ARF. See paragraphs 0031-0035, 0037-0040, 0081, claims 4 and 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al., US 5,747,469 in view of either or both of Lu et al. (Cancer Res. 62: 1305-1310, 01 March 2002) or Tango et al. (Hum. Gene Ther. 13: 1373-1382, 20 July 2002) further in view of Almond et al., WO 99/47690.

Roth describes viral vectors, such as retrovirus, adenovirus, AAV, HSV, or CMV vectors, or non-viral vectors in liposomal formulations, and methods of treating tumors or cancer in an individual, such as skin, lung, and breast cancer by administration of the vector to tumors and also treating the patient with chemotherapy or radiation therapy. See entire document, especially the claims. Roth does not teach including a p14ARF gene on the vector, i.e. a bicistronic construct or vector.

However, Lu disclosed that tumors without a p53 mutation are often resistant to p53 gene therapy (page 1305). Lu disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2, whose expression is induced by p53, and which is inhibited by ARF (page 1307, col. 2). Lu showed that co-transfection with separate vectors encoding p14ARF and p53 was significantly more effective at inducing cell death in tumor cell lines (page 1306). Lu taught that co-expression of p53 with ARF in gene therapy will be more effective for tumors that have p53+ tumor cells (page 1309, col. 1).

Also, Tango disclosed that co-transfection of tumor cells both *in vitro* and *in vivo* with vectors (administered simultaneously) expressing p14ARF (the human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy. Like Lu, Tango taught that ARF inhibits MDM2, which then reduces or eliminates increased degradation of p53. See entire document, especially pages 1380-1381.

Neither Lu nor Tango suggests including both the p53 and p14ARF genes on a bicistronic construct or vector.

However, Almond et al. generally describes the treatment of cancer with two or more genes at the same time, which augments the action of one or both genes. It teaches that the use of separate vectors, each encoding a different therapeutic gene, presents a variety of problems including immunogenicity, oncogenicity, and reduced transduction efficiency (page 3). Almond discloses that these problems can be reduced by introducing both therapeutic genes, e.g.

including a p53 gene, on a single vector, such as an adenovirus, AAV, herpesvirus, or retrovirus vector or in a liposome, which ensures that both genes are expressed in the same cells. The genes may either be present in the vector in separate expression cassettes, i.e. each under control of a different promoter, or they can be present in a single expression cassette under control of the same promoter with an IRES separating the genes. (See pages 4-10, 84 for overview). Almond also teaches that the multi-gene therapy can be combined with radiation therapy or chemotherapy (page 91).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a p14ARF gene on the vector of Roth, either under control of the same promoter as the p53 gene with an IRES between the p53 and ARF genes, or under control of a different promoter than that of the p53 gene. (Either arrangement meets the limitation of a bicistronic construct). One would have been motivated to include the p14ARF gene because Lu and Tango taught that co-expression of p14ARF with p53 improved the effectiveness of the p53 by blocking the inhibitory effects of MDM2 on p53. Both taught that the combination would be more effective than p53 gene therapy alone. From the teachings of Almond, one would have been motivated to include both the p53 and p14ARF genes on the same vector to avoid the problems associated with using separate vectors in gene therapy, and to improve the efficiency of the gene therapy.

Double Patenting

Applicant is advised that should claims 2 and 3 be found allowable, claims 4 and 5, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). While claims 2 and 3 are directed to the bicistronic construct itself, rather than the vector or delivery vehicle containing it of claims 4 and 5, claims 2 and 3 cover the same thing since the presence of the remainder of the vector is required in claims 2 and 3.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe, Ph.D.
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Art Unit 1633